REMARKS

REQUEST FOR EXAMINER INTERVIEW

Applicant respectfully requests an Examiner interview before issuance of an office action. In particular, Applicant is eager for suggestions to put claim 30 in condition for allowance.

STATUS OF THE CLAIMS

Claims 8, 9, 12, 14-19, 23, 26, 28, 29, and 30 were pending in this application. Claims 8 and 30 have been amended. Following the amendments, claims 8, 9, 12, 14-19, 23, 26, 28, 29, and 30 will be pending and at issue.

SUPPORT FOR AMENDMENTS TO THE CLAIMS

Claim 8 has been amended to recite "attenuated T-cell lines" instead of "attenuated T-cells" to more clearly define the invention, e.g., a method of mediating an immune response using a T-cell lines, e.g., polyclonal T-cells, e.g., non-cloned T-cells. Support can be found throughout the specification as filed, e.g., page 7, line 11; page 9, last paragraph (describing the composition of the invention to be a polyclonal set of T-cells "activated against epitopes" (plural) and inducing a response against "many different pathogenic T-cells."); page 10, line 21 ("To establish T-cell lines … "); page 11, line 3 ("T-cell lines were re-stimulated …"); and page 12, line 20 ("… were considered as responding T-cell lines.") and the described method for making the vaccine which does not include a clonal step, e g., a step of limiting dilution.

In addition, the method for preparing T-cells recited in Claim 30 necessarily results in T-cell lines, e.g., polyclonal T-cells, e.g., non-cloned T-cells.

Claim 30 has been amended to further clarify recitation of one embodiment of Applicant's invention, e.g., a method using attenuated T-cells prepared as described in one example of the instant application. Support can be found throughout the specification as filed, e.g., page 8 and Example 1, pages 10 and 11.

The amendments to the claims therefore add no new matter and entry is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (WRITTEN DESCRIPTION)

Claim 30 was rejected under 35 U.S.C. § 112, first paragraph (a new matter rejection). The Examiner stated that:

> As set forth previously, The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, the recitation of:
>
> A) The method comprising the specific steps set forth in Claim 30. Note: including the new steps of the 2/07/07 amendment.
>
> Applicant's arguments, filed 2/07/07 have been fully considered but they are not persuasive. Applicant argues that new amendments to the claim recite language from Example 1 of the specification and do not comprise the introduction of new matter.
>
> A review of the example shows that Applicant has used some of the language of the example, but not all of it. For example, the first sentence of Example 1 discloses that it encompasses only a method of treating secondary progressive MS, yet the claim does not recite this limitation. Further, the Example discloses vaccination with 40 x 106 cells and vaccination intervals of 3 months or 6 weeks, limitations not found in the claim. Accordingly, the specification cannot support the method as claimed.

Without agreeing with the Examiner's rejection but rather to further prosecution, Applicant has amended claim 30 to recite the noted limitations. Withdrawal of the rejection is requested.

Claims 8, 9, 12, 14-19, 23, 26, 28, and 30 were rejected under 35 U.S.C. 112, first paragraph (a new matter rejection). Applicant respectfully disagrees. The Examiner stated that:

> As set forth previously, The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:
>
> A) T cells are cultured in the presence of whole bovine myelin proteins or synthetic human proteins (Claims 8 and 30).
>
> B) T cells that respond to a plurality of different myelin proteins (Claim 11).
>
> C) T cells are reactive to a plurality of different myelin proteins (Claim 23).
>
> Regarding A), Applicant cites page 8 of the specification for support.
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> At page 8 the specification discloses PBMCs are cultured in the presence of cow myelin proteins or synthetic complete human proteins.

> Regarding B) and C), Applicant cites pages 8 and 11 of the specification for support.
>
> At page 8 the specification discloses PBMCs are cultured in the presence specific myelin antigens. Page 11 discloses a specific example in which PBMCs and myelin antigens are employed.
>
> Applicant's arguments, filed 2/07/07 have been fully considered but they are not persuasive. Applicant argues that the specification teaches "T cells" at numerous cites.
>
> While the specification may disclose vaccines comprising T cells, the method of making the vaccine comprising T cells recited in the claims employs PBMCs.

Without agreeing with the Examiner's rejection but rather to further prosecution, Applicant has amended claim 30 to recite PBMCs. Withdrawal of the rejection as drawn to claim 30 is requested.

Turning to the remaining claims, Applicant reiterates the arguments from the response filed February 7, 2007 and incorporates those arguments by reference. At numerous points in the specification, including the claims as filed, Applicant used the terminology "T-cells" to describe the claimed invention, including methods of making the vaccine. For example, at page 8, lines 4-5, Applicant stated "Preferably, T-cells are removed from the patient by leukaphoresis." One of skill understands that "preferably" indicates that T-cells can be derived from PBMCs (e.g., are removed from the patient by leukaphoresis). "Preferably" does not indicate that the T-cells must be derived from PBMCs.

Further, what is conventional or well known to one skilled in the art need not be disclosed in detail. The fact that T-cells can be derived from a variety of sources including, e.g., PBMCs and CSF, is well-known to one of skill in the art and therefore did not need to be explicitly disclosed in the specification. In addition, one of skill in the art readily understands that the described method for making the vaccine can be modified to use non-PBMC sources of T-cells.

Applicant respects withdrawal of this rejection as drawn to the remaining claims.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 8, 9, 12, 14-19, 23, 26, 28, and 30 were rejected under 35 U.S.C. 103(a) each as allegedly unpatentable over Stinissen et al. (1996) in view of Correale et al (1995) and the

background teachings of the specification. Applicant respectfully disagrees.

The combination of art does not include each and every element of the claims

The combination of Stinissen and Correale do not render any of the pending claims obvious because the combination of art does not include the element of "polyclonal subset" or "T-cell lines." The claimed method uses T-cells that are polyclonal, e.g., T-cell lines. The population of T-cells that are injected into a patient include T-cells that react with multiple different myelin antigens, and multiple types of T-cells that react with each myelin antigen. This is the necessary result of preparing the T-cells using the method describe by Applicant and without a cloning step as described by Stinissen. To more clearly define Applicant's invention, Applicant has amended claim 8 to recite "T-cell lines." Previously presented claim 30 included the element "polyclonal subset."

In addition, amended Claim 30 recites "A method of treating secondary progressive multiple sclerosis in a human …" Stinissen does not teach of method of treating secondary progressive MS. Instead, on page 506, Stinissen teaches that "In three vaccinated patients with chronic progressive MS, no obvious effects on the clinical course were seen."

Correale does not remedy the deficiencies of Stinissen. The prima facie case of obviousness in not made, and withdrawal of this rejection is respectfully requested.

No expectation of success

Assuming that the combination of art cited against the claims does contain all the claim elements (and Applicant does not concede that it does), one of skill in the art would have had no expectation of success when combining the elements.

One of skill in the art would have had no expectation of success when combining the clonal method taught by Stinissen with the additional MS myelin antigens taught by Correale. As noted previously by Applicant, support for this argument can be found in a subsequent publication by the same group that authored Stinissen, VAN DER AA (Van der AA et al (2003) T cell vaccination in multiple sclerosis patients with autologous CSF-derived activated T cells: results from a pilot study. Clin Exp Immunol 131:155-168) First, the authors of VAN DER AA

describe the "TCV protocol" using MBP specific clonal T cells as described in Stinissen. Then, on page 156, first full paragraph, the authors describe how generating a T-cell vaccine specific for more than one myelin antigen and using the techniques described in Stinissen is "almost impossible:"

> Increasing evidence indicates that T cells recognizing other myelin component may also contribute to the disease process in MS. Experiments in EAE and studies in human T cell reactivity demonstrated that PLP and MOG may play an important role as candidate myelin antigens in the autoimmune mediated demyelination. Incorporating T cell populations specific for these autoantigens in the vaccines may improve the effectiveness of the current TCV protocol. However, technically it is almost impossible to generate T cell clones specific for three different myelin antigens with the current protocol design. (Emphasis added)

The T-cell vaccine described in VAN DER AA does not use a clonal method. Given that Stinissen describes the critical need for T-cell cloning in generating a T cell vaccine, and that a subsequent publication by the same group describes the impossibility of a T cell vaccine directed to multiple myelin antigens using the clonal method, and experiments that do not use a clonal method, one of skill would have had no expectation of success when combing Stinissen and Correale. The prima facie case of obviousness in not made, and withdrawal of this rejection is respectfully requested.

Rebuttals to the Examiner's rejections

In the Office Action, the Examiner stated:

> Stinissen et al. teaches a method of mediating an immune response comprising administering subcutaneously irradiation-attenuated T-cells derived from autologous peripheral mononuclear cells (comprising T cells) cultured in the presence of natural or synthetic human myelin proteins (see particularly page 503, T CELL VACCINATION IN MS).
>
> The reference differs from the claimed invention only in that it does not teach the use of attenuated T cells that target more than one myelin protein and in that it does not teach the optimization of the claimed method as set forth in dependent Claims 16-19.

Applicant disagrees. Stinissen also differs from the invention in that the method described by Stinissen uses cloned T-cells. In contrast, the Applicant's invention uses polyclonal

T-cells, e.g., a heterogeneous population of T-cells for each antigen. This is a necessary result of the method for producing the T-cells that was recited in previously examined Claim 30.

In the Office Action, the Examiner stated:

> A review of the instant claims shows that they comprise a method of treating MS employing a product-by-process. In such instances the process by which the product is produced is considered irrelevant to the method of treating unless said process results in a product that would comprise patentably distinct treatment properties. In the instant case the claims are simply read as reciting a method of treating MS by administering attenuated T cells reactive to a plurality of different bovine or human myelin proteins.

Applicant disagrees. Claim 30 (both before and after the current amendment) recites a method for making the vaccine that results in a polyclonal mixture of T-cells to multiple antigens; e.g., more than one T-cell species to each antigen. In contrast, the method disclosed by Stinissen uses a clonal technique, e.g., a single T-cell species to each antigen. The product is patentably distinct. Therefore, the process by which the vaccine is produced is not irrelevant to the method of treating.

In the Office Action the Examiner stated:

> Applicant argues that Stinissen et al. teaches away from the claimed method.
>
> A review of the reference reveals only that highly purified T cells are necessary for use in the treatment of MS. There is no teaching that said purified T cells cannot be produced.

Applicant repeats the point that Stinissen teaches away from the method as claimed and described by Applicant – using T-cell lines, e.g., polyclonal T-cells, e.g., non-cloned T-cells. Stinissen described the necessity of cloning the T-cells, e.g., generating highly purified T-cell clones. As described by Stinissen, page 503, middle of the first paragraph:

> This T cell cloning method is very critical in the vaccine preparation since only highly purified T cell clones can be expanded to the number of cells need for vaccination. (Emphasis added)

A single highly purified T-cell clone, as taught by Stinissen, by definition cannot include more than one polyclonal set of T-cells wherein each set includes more than one kind of T-cell and each set that respond to a different protein, as described and claimed by Applicant.

In the Office Action the Examiner stated that:

> Applicant cites Van der Aa, A., et al. (2003) as teaching that it would be almost impossible to generate T cell clones specific for three different myelin antigens.
>
> A review of the reference discloses that the statement regarding the difficulty of generating T cell clones specific for three different myelin antigens is made in the Introduction section of the reference with no explanation. Indeed, the next paragraph teaches that the authors were able to do that very thing, i.e., the generation of sufficient T cells for vaccination, with no particular difficulty. Accordingly, the isolated statement regarding difficulty in generating T cell clones would not lead the skilled artisan to doubt the expectation of success with the claimed method.

Applicant disagrees. The authors of Van der AA did not use a clonal approach to generate sufficient T-cell lines for vaccination. As described on page 157 (Generation of CSF derived activated CD4+ T cell vaccines) the authors of Van Der AA used an approach similar that described by Applicant, e.g., stimulation and expansion of a heterogeneous population of T-cells, e.g., CSF.

In conclusion, the combination of art does not include all elements of the claims and one of skill in the art would have no expectation of success when combining the cited art. Therefore, a prima facie case of obviousness is not made. Withdrawal of this ground of rejection of the claims is respectfully requested.

CONCLUSION

Withdrawal of the pending rejections and reconsideration of the claims are respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is invited to telephone Applicant's representative at (415) 875-2316.

Respectfully submitted,
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